

Original article

Lifestyle Changes Lower FABP4 Plasma Concentration in Patients With Cardiovascular Risk

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Article history:

Received 6 May 2011

Accepted 18 September 2011

Available online 5 December 2011

Keywords:

FABP4

Body weight loss

Physical activity

ABSTRACT

Introduction and objectives: To analyze the impact of lifestyle changes on adipocyte fatty acid-binding protein (FABP4) plasma levels in patients with cardiovascular risk.

Methods: A 1-year prospective study enrolled 140 patients with cardiovascular risk but without previous cardiovascular disease to evaluate the impact of therapeutic lifestyle changes on cardiovascular risk, focusing on tobacco, nutrition education, and physical activity.

Results: The FABP4 variation was inversely associated to physical activity changes (MET-h/wk). FABP4 significantly decreased in patients with increased physical activity, whereas it increased with physical activity reduction. These FABP4 changes were also associated with modifications in body mass index and insulin resistance parameters; however, the correlations between physical activity and FABP4 remained after adjusting for these confounding variables. Changes in physical activity were the main predictors of FABP4 modifications. FABP4 reductions were directly associated with low-density lipoprotein-cholesterol and apolipoprotein B reductions. Neither tobacco cessation nor diet composition modified FABP4 concentrations.

Conclusions: Increasing aerobic physical activity can decrease FABP4 plasma levels, independently of weight reduction. If a causal role of FABP4 in metabolic and vascular alterations could be established, our results would add new positive effects on metabolic and cardiovascular risk of both physical activity and avoiding obesity.

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Cambios de estilo de vida disminuyen las concentraciones plasmáticas de FABP4 en pacientes con riesgo cardiovascular

RESUMEN

Introducción y objetivos: Analizar el impacto de cambios de estilo de vida en la concentración plasmática de adipocyte fatty acid-binding protein (FABP4) en pacientes con riesgo cardiovascular.

Métodos: Se incluyó a 140 pacientes con riesgo cardiovascular sin enfermedad cardiovascular previa en un estudio prospectivo de 1 año de duración para evaluar el impacto de cambios terapéuticos de estilo de vida (tabaco, educación nutricional y actividad física) en el riesgo cardiovascular.

Resultados: Las variaciones de la FABP4 se asociaron inversamente con cambios en la actividad física (MET-h/sem). La FABP4 se redujo significativamente en los pacientes que aumentaron su actividad física, mientras que aumentó en quienes la disminuyeron. Los cambios observados en la FABP4 también se asociaron con modificaciones en el índice de masa corporal y la resistencia a la insulina; sin embargo, las correlaciones entre actividad física y FABP4 permanecieron significativas tras ajustarlas por variables de confusión. Los cambios en la actividad física fueron los principales predictores de las modificaciones en la FABP4. La disminución de FABP4 se asoció directamente con reducciones de colesterol ligado a las lipoproteínas de baja densidad y apolipoproteína B. Dejar de fumar y la composición de la dieta no modificaron las concentraciones de FABP4.

Conclusiones: La concentración plasmática de FABP4 puede reducirse aumentando la actividad física aeróbica. La actividad física actúa sobre las concentraciones de FABP4 independientemente de la reducción de peso. Si se pudiera establecer un papel causal de la FABP4 en las alteraciones metabólicas y vasculares, nuestros resultados añadirían un nuevo efecto positivo tanto de la actividad física como de la reducción de la obesidad en el riesgo metabólico y cardiovascular.

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Palabras clave:

FABP4

Pérdida de peso

Actividad física

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Abbreviations

CV: cardiovascular
 FABP4: adipocyte fatty acid-binding protein
 PA: physical activity

INTRODUCTION

The adipocyte fatty acid-binding protein (FABP4), also known as aP2, is predominantly expressed in the adipose tissue, and it is one of the most abundant proteins in the cytoplasm of adipocytes and macrophages.¹ A FABP4 deficiency in animal models is linked to reduced lipolysis² and protects from hyperinsulinemia, hyperglycemia, and insulin resistance in induced-obesity models³ and from atherosclerosis in hypercholesterolemic mouse models.⁴ Additionally, Furuhashi et al. demonstrated that an inhibitor of FABP4 improves type 2 diabetes control and protects against severe atherosclerosis in apolipoprotein (apo) E deficient mice.⁵ In humans, FABP4 has been detected in the circulation,⁶ but its biological function is not yet clearly understood. Circulating FABP4 concentrations are associated with anthropometric variables and body fat distribution and are increased in overweight and obese compared to lean subjects.⁶ Paradoxically, circulating FABP4 levels increase during profound fat mass loss induced by bariatric surgery.⁷ It has been proposed that FABP4 is a marker of increased lipolytic activity in this situation. In addition, FABP4 levels have been suggested as a predictor of type 2 diabetes and metabolic syndrome development, independent of obesity and insulin resistance.^{8,9} There is indirect evidence that circulating FABP4 could mediate insulin resistance and atherogenic dyslipidemia and promote inflammation.^{10,11} Increased circulating FABP4 has been associated with carotid intima-media thickening,¹² with the number of stenotic coronary arteries,¹³ and with a greater coronary plaque burden assessed by intravascular sonography.¹⁴ Moreover, a FABP4 genetic variant has been associated with reduced risk of cardiovascular (CV) disease.¹⁵

Considering that high FABP4 plasma levels could contribute to metabolic and vascular alterations, investigating the mechanisms associated with FABP4 plasma level reductions is warranted. Little research has addressed the impact of drugs on circulating FABP4 levels. In diabetic subjects, thiazolidinedione treatment has been linked to increases in FABP4 levels.¹⁵ Fenofibrate treatment has no effect,¹⁶ whereas atorvastatin reduces FABP4 levels in hyperlipidemic subjects.¹⁷ Despite the observation that FABP4 seems to be closely associated to adiposity and fat distribution, data about the impact of lifestyle changes on FABP4 are scarce. Reductions in FABP4 have been shown during early refeeding of female subjects with anorexia nervosa in parallel to weight gain and concomitant gain in fat mass.¹⁸ One study postulated that changes in FABP4 levels may discriminate between permanent and temporary body weight loss in response to diet restriction.¹⁹ Only 2 studies, conducted in healthy Asian women²⁰ and obese children,²¹ have prospectively investigated the impact of physical activity (PA) and diet on FABP4, and they showed that weight loss was linked to FABP4 reduction. However, a similar study in obese polycystic ovary syndrome women produced no effects on circulating FABP4.²²

Leisure-time PA levels are low in Southern Europe countries²³ and it has been shown that sedentary lifestyle and abdominal

obesity are associated with increased CV risk.²⁴ No studies concerning the impact of a global lifestyle change on FABP4 levels have been performed in adult men and women with elevated CV risk. Considering the effect of FABP4 on metabolic and vascular processes, therapeutic actions that decrease their levels would be of great clinical interest.

METHODS

Patients and Study Design

The study included 140 patients, 105 men and 35 women, aged 22 to 79 years, with abdominal obesity and increased global CV risk who attended the vascular medicine and metabolism unit of our hospital and were participating in a prospective study on the impact of therapeutic lifestyle changes on CV risk.²⁵ Patients were advised to follow a therapeutic lifestyle change focusing on increased leisure PA, proper nutrition, and smoking cessation. They were evaluated before and after a 1-year intervention period. The inclusion criteria were abdominal obesity (≥ 102 cm men; ≥ 88 cm women) and increased global CV risk because of type 2 diabetes or a global CV risk according to a 10-year Framingham Risk Score between 5% and 20%. Patients with previous CV disease, neoplasm antecedents, or other severe chronic disease were not included. The usual pharmacologic treatment was maintained or modified as necessary according to clinical indications.

A complete physical, anthropometry, general biochemical, and vascular evaluation was performed before and after the intervention period and FABP4 plasma levels were measured before and after a 1-year follow-up. The ethics committee of the hospital approved the study and all subjects gave written informed consent.

Therapeutic Lifestyle Changes

Patients were advised to follow a Mediterranean-type diet. Diet was evaluated by frequency questionnaires and 24-h recall records over 3 days. Leisure-time PA was assessed by the validated Minnesota Questionnaire, adapted to the Spanish population, at baseline and at 1-year follow-up. All participants were advised to increase their PA by performing low-to-moderate intensity aerobic activities for 30 to 45 min, 5 times per week. The recommended activities included walking at a moderate pace, stationary cycling, or leisurely swimming. PA was expressed as metabolic equivalent hour per week (MET·h/wk). Levels of total PA were categorized as low (< 20 MET·h/wk), moderate (20–40 MET·h/wk) and high (> 40 MET·h/wk) before and after follow-up. Patients were classified into 3 groups according to changes in PA level after the follow-up period, based on increasing, maintaining, or decreasing PA.

Smoking status was determined by the standard questionnaires when indicated. Smokers were advised to stop tobacco consumption and pharmacological and psychological support was given when necessary. Follow-up medical and dietician visits were performed at 4-month intervals.

Biochemical Determinations

Plasma levels of FABP4 were determined by commercial ELISA kits (Bio Vendor Laboratory Medicine Inc., Brno, Czech Republic). The precision of this assay was 5.3% intra-assay and 3.9% inter-assay coefficients of variation. The antibodies used in the human FABP4 ELISA are highly specific for human FABP4, with no

detectable cross-reactivity to human FABP1, FABP2, FABP3 or FABP5.

Standard biochemical parameters were determined via the usual methods. Cholesterol, triglycerides, apo A-1, apo B-100, apolipoprotein B100, direct low density lipoprotein-cholesterol and high density lipoprotein-cholesterol were measured using enzymatic and immunoturbidimetric assays (Spinreact, SA, Spain) adapted to the Cobas Mira Plus autoanalyzer (Roche Diagnostics, Spain).

Statistical Analysis

Statistical tests and corresponding *P*-values were 2-sided. In all cases, a *P*-value of less than .05 was considered statistically significant. All statistical analyses used SPSS version 17.0 (SPSS Inc., Chicago, Illinois, United States). Normality distribution was assessed with the Kolmogorov-Smirnov test. Log-transformation was performed before analyses when variables had a skewed distribution. Spearman correlation tests were used to analyze bivariate associations between changes in FABP4 and changes in other variables. Partial bivariate correlation tests were used to adjust bivariate associations by changes in weight or body mass index. Data from baseline and at a one-year follow-up are presented as mean (standard deviation) or as the median [25th percentile- 75th percentile] for normally distributed continuous variables and for skewed distributed continuous variables, respectively, and as frequencies for categorical variables. The observed within-group differences of variables before and after the intervention period were analyzed using a nonparametric paired test, Wilcoxon or chi-squared, as appropriate. Changes in variables were calculated as 1-year follow-up values minus baseline values. The effects of intervention on different continuous variables between-groups were assessed by comparing changes in variables using Mann-Whitney U tests. One-way ANOVA was used for comparisons of FABP4 between smokers and nonsmokers at baseline.

Backward stepwise multiple linear regression analyses were performed to find the changes in variables with an independent significant association with changes in FABP4. Variables with a high association ($r > 0.700$, $P < .05$) were not included in the same model. Models included changes in FABP4 as dependent variable and changes in apo A-1, changes in PA, and changes in anthropometric variables as independent variables. The accepted model was that with a higher adjusted R^2 and lower number of variables included. The final parameters were obtained introducing the chosen variables in a multiple linear regression analysis. We report the B coefficient values and their 95% confidence interval (95%CI).

RESULTS

Table 1 shows basal and postintervention values of anthropometry, PA, energy intake, lipids, and pharmacological treatment of patients distributed according to their PA change category. We observed that changes in circulating FABP4 levels were inversely correlated with changes in PA in the whole group ($r = -0.171$, $P = .044$) (Fig. 1). Moreover, this association between PA and FABP4 was enhanced when excluding participants who did not change their PA ($r = -0.348$, $P = .024$) (Fig. 1). Increments of FABP4 correlated positively with increments of weight ($r = 0.211$, $P = .012$), waist circumference ($r = 0.190$, $P = .024$), and body mass index ($r = 0.213$, $P = .011$) in all participants. The association between PA and FABP4 reductions was much lower but conserved statistical significance after adjusting for weight and body mass index

changes ($r = -0.167$, $P = .050$, and $r = -0.184$, $P = .030$, respectively). Changes in FABP4 levels were also inversely correlated with changes in apo A-1 levels ($r = -0.201$, $P = .017$) and positively correlated with changes in insulin levels ($r = 0.207$, $P = .014$) in all participants. All of these associations were lost in the group of patients with increasing PA. However, the nonincreasing PA group maintained the positive associations between changes in FABP4 and changes in insulin and anthropometric variables.

Figure 2 shows the changes in circulating FABP4 levels regarding the 3 categories of PA modification. Increasing PA compared to maintaining or even decreasing PA, significantly reduced FABP4 levels. Moreover, independently of the initial levels of PA, increasing vs decreasing PA accounted for an average decrease of FABP4 levels of 10.3 units ($P < .015$). The reduction in FABP4 levels observed in the increasing PA group was directly associated with a reduction in apo B-100 and low-density lipoprotein-cholesterol levels ($r = 0.491$, $P = .017$ and $r = 0.539$, $P = .008$, respectively).

As expected, in the decreasing PA group, weight and body mass index increased significantly ($P = .002$ and $P = .020$, respectively), and the same trend was observed for waist circumference ($P = .123$) (Table 1). These parameters were not modified in the maintaining PA group whereas in the increasing PA group, waist circumference, weight, and body mass index were significantly lowered ($P = .009$, $P = .003$ and $P = .004$, respectively) (Table 1). Moreover, increasing MET-h/wk inversely correlated with variations in weight ($r = -0.407$, $P < .001$), waist circumference ($r = -0.359$, $P < .001$), and body mass index ($r = -0.405$, $P < .001$). However, those patients who reduced weight without changes in PA (the maintaining PA group) showed no changes in their circulating FABP4 levels after the intervention period (30.6 [95%CI, 25.9-35.2] $\mu\text{g/l}$ at 1-year follow-up vs 31.3 [95%CI, 27-35.6] $\mu\text{g/l}$ at baseline, $P = .556$). Those patients who increased PA without changes in weight showed reduced circulating FABP4 levels after the intervention period (28 [95%CI, 8.5-47.5] $\mu\text{g/l}$ at 1-year follow-up vs 34.7 [95%CI, 9.7-59.8] $\mu\text{g/l}$ at baseline, $P = .046$). Total caloric intake was not altered during the study regardless of the PA group (Table 1). Dietary parameters were not significantly associated with FABP4 modifications (data not shown).

There were no differences in FABP4 levels between smokers and nonsmokers (29.2 [95%CI, 24.9-33.4] $\mu\text{g/l}$ vs 29.6 [95%CI, 26.7-32.5] $\mu\text{g/l}$, respectively, $P = .605$) at baseline and quitting smoking was not associated with changes in FABP4 levels ($P = .541$).

Finally, stepwise multiple regression analyses were performed to evaluate the independent predictors of changes in FABP4 levels. In all participants, changes in apo A-1 and in PA were the independent factors associated with FABP4 changes ($B = -0.166$ [95%CI, -0.333 to -0.001], $P = .050$ and $B = -0.116$ [95%CI, -0.212 to -0.019], $P = .019$, respectively). Excluding from the analyses those participants with no changes in PA, changes in apo A-1 and in PA were also the independent factors associated with FABP4 changes ($B = -0.409$ [95%CI, -0.812 to -0.006], $P = .016$ and $B = -0.206$ [95%CI, -0.371 to -0.040], $P = .047$, respectively). Changes in PA were the main contributor (15%) to FABP4 changes. In all cases, generated models showed that changes in any of the measured anthropometric variables were not significantly associated with changes in FABP4.

DISCUSSION

This study is the first to show that an increase in PA, regardless of weight loss, during a therapeutic lifestyle change program, leads to a decrease in circulating FABP4 in patients with CV risk. Weight loss was also associated with FABP4 reduction. Variations in other

Table 1

Participant Characteristics at Baseline and After One-Year Intervention Divided by Categories of Changes in Physical Activity

Variables	Decreasing PA (n=19)		Maintaining PA (n=98)		Increasing PA (n=23)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
<i>Clinical data</i>						
Sex (men, %)	79		71		87	
Age, years	55±9		54±10		53±10	
Weight, kg	91.4±10.8	94.1±11.6*	87.9±14.3	87.7±15.3	88.9±11.5	86.3±12.1*
Body mass index, kg/m ²	32.8±4.1	33.7±4*	31.4±3.7	31.3±4	31.5±3.3	30.5±3.5*
Waist circumference, cm	107.1±8	108.2±7.6	105.6±9.3	104.8±10.4	103.4±7.5	99.9±8.1*
<i>Lifestyle parameters</i>						
PA, MET·h/wk	43.3 [33.2-49.9]	19.6 [15.3-37.1]*	16.5 [6.5-41.5]	18.7 [5.6-46.2]*	16 [10.5-26.8]	41.3 [27.5-50.7]*
E intake/E requirements	0.96±0.24	0.9±0.21	1.04±0.32	0.98±0.26	1±0.3	1.02±0.16
<i>Biochemical parameters</i>						
Total-cholesterol, mmol/l	5.4±1.3	5.1±1.6	5.3±1.2	5.2±1.4	5.4±1.4	5.2±0.9
LDL-cholesterol, mmol/l	3.6±1.2	3.2±1.3	3.3±0.8	3.1±0.9*	3.2±0.9	3.3±0.8
HDL-cholesterol, mmol/l	1.3±0.2	1.3±0.3	1.3±0.3	1.3±0.3	1.4±0.3	1.4±0.3
Triglycerides, mmol/l	2.3 [2-3.3]	1.9 [1.6-3.5]	2.5 [1.9-3.6]	2.1 [1.5-3.2]	1.7 [1.2-3.3]	1.9 [1.1-2.7]
Apolipoprotein A-1, mg/dl	130±13	131±12	133±14	135±13	133±14	138±17*
Apolipoprotein B-100, mg/dl	124±30	114±32	118±21	117±37	114±23	114±22
<i>Medications</i>						
Statins, %	32	63*	50	55	56	78
Fibrates, %	32	21	39	46	43	30
Antihypertensive drugs, %	53	58	37	42	43	48
Oral antidiabetic drugs, %	37	47	20	21	9	13

E, energy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET·h/wk, metabolic equivalent hour per week; PA, physical activity.

Values are means±standard deviation or median [interquartile range] or frequencies.

**P*<.05 for the comparison of measures at baseline and follow-up by the nonparametric paired-samples Wilcoxon test for continuous variables or by the chi-squared test for categorical variables in each category of PA evolution.

components of the therapeutic lifestyle changes, such as smoking and diet, did not contribute to FABP4 modifications. Our group and others have already communicated that FABP4 is associated with body fat mass.^{6,11} It has been suggested that FABP4 changes reflect

fat mass dynamics and nutritional status.^{7,18,19} Because PA was also associated with body weight reduction in our study, it would be logical to consider that the impact of PA on FABP4 levels could be mediated by fat mass reduction. However, in our study, the

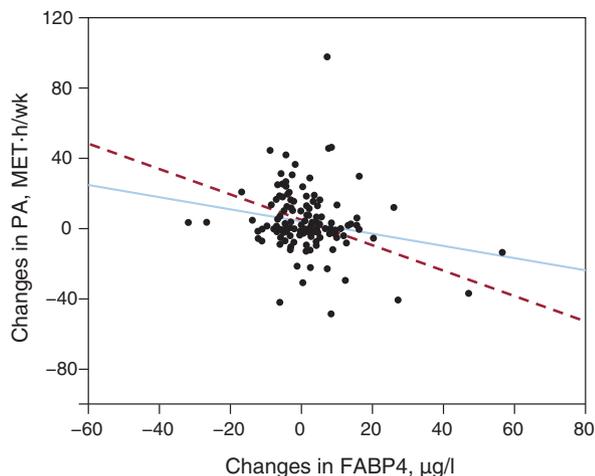


Figure 1. Association of changes in circulating FABP4 levels (1-year follow-up FABP4 value minus baseline FABP4 value) with changes in physical activity (1-year follow-up MET·h/wk value minus baseline MET·h/wk value). Red line = participants with changes in physical activity (n=42). Blue line = all participants (n=140); FABP4, adipocyte fatty acid-binding protein; MET·h/wk, metabolic equivalent hour per week; PA, physical activity.

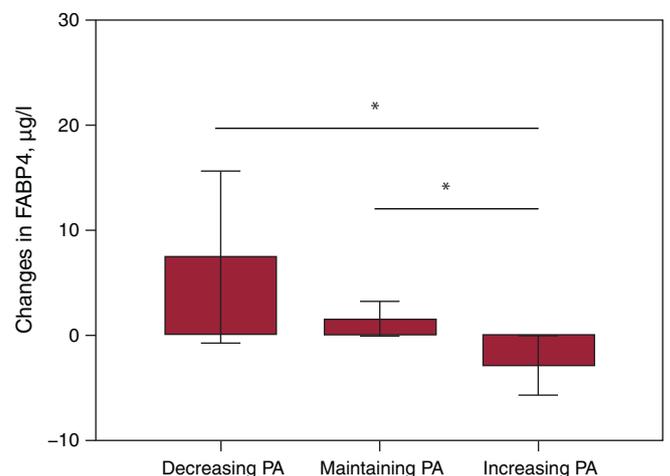


Figure 2. Column plot showing changes in circulating FABP4 levels (1-year follow-up FABP4 value minus baseline FABP4 value) in decreasing (n=19), maintaining (n=98), or increasing (n=23) physical activity groups of patients. FABP4, adipocyte fatty acid-binding protein; PA, physical activity. **P*<.05 for the comparisons between categories of physical activity evolution.

inverse correlation between PA and FABP4 remained after adjustment for body weight reduction. Moreover, those subjects who reduced their weight without increasing PA did not modify their FABP4 levels, and conversely, those patients who increased their PA without succeeding in lowering weight significantly decreased their FABP4 levels. In a regression analysis, only the change in PA, independent of changes in weight, waist circumference, or body mass index, was the determinant of FABP4 changes. Thus, we consider that increasing PA reduces FABP4 independently and additionally to the effect of weight loss. In line with our results, Choi et al. and Reinher et al. showed a decrease in FABP4 levels after physical training and weight loss in a group of obese women and children, respectively,^{20,21} whereas Möhlig et al. observed no FABP4 changes after a 4-month lifestyle intervention in polycystic ovary syndrome patients.²² Moreover, FABP4 increased in the decreasing PA group, despite being the group in which statins treatment was significantly increased.

The mechanisms responsible for changes in circulating FABP4 remain unknown. Interestingly, it has been observed that endurance exercise training is associated with increased accumulation of FABP4 in skeletal muscle fibers,^{24,26} probably due to an increased lipolysis in the tissue, or perhaps a higher retention of FABP4 in tissue could result in its plasma reduction.

As expected, FABP4 variations were directly correlated with increases in body fat and insulin function parameters. Interestingly, in those patients increasing PA, these correlations were lost whereas strong associations were observed between FABP4 changes and low-density lipoprotein-cholesterol and apo B-100 variations. The association between FABP4 and lipid metabolism has been previously reported. We have communicated an association between FABP4 and atherogenic dyslipidemia in type 2 diabetic patients.¹⁰

CONCLUSIONS

In conclusion, knowledge of mechanisms regulating circulating FABP4 reductions, such as increasing PA and weight loss, will allow for new therapeutic strategies to prevent metabolic and vascular risk in obese patients.

Limitations

Sample size of the study is limited, precluding a better involvement of PA in the observed biochemical effects due to the limitation on performing comprehensive multivariable analysis.

FUNDING

This work was supported by grants from the *Fondo de Investigación Sanitaria* (PI051954 and PI081409) and CIBER in Diabetes and Associated Metabolic Disorders (ISCIII, *Ministerio de Ciencia e Innovación*, Madrid, Spain).

CONFLICTS OF INTEREST

None declared.

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